

# Proposed Nasopharyngeal Cancer Mode of Action for Formaldehyde Based on EPA Cancer Guidelines (1)

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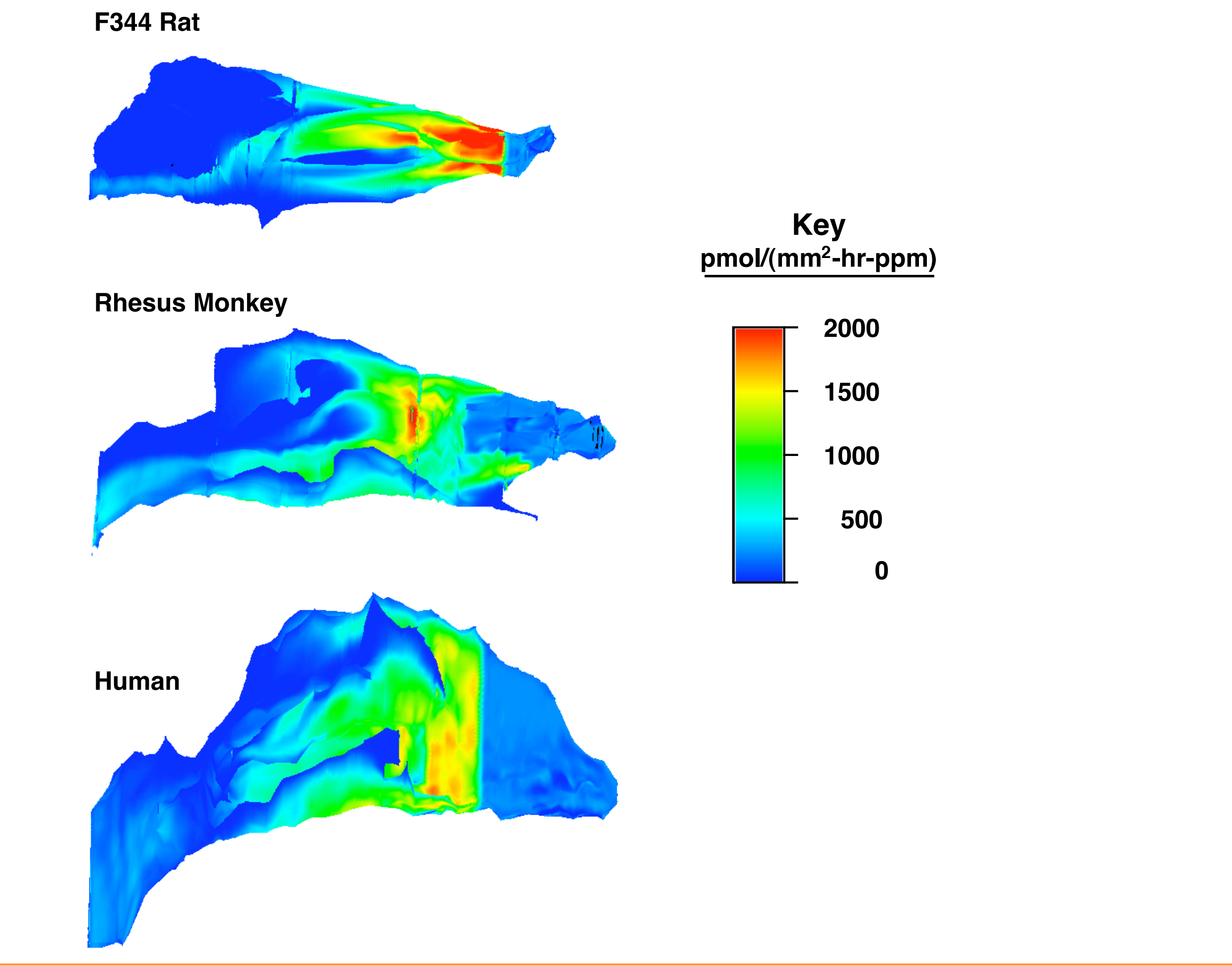
## Introduction

Formaldehyde is a known human carcinogen. Human epidemiological studies report increased oronasal and nasopharyngeal carcinomas in formaldehyde exposed workers. This occupational exposure to formaldehyde has been associated with the undifferentiated and squamous cell carcinoma (SCC) forms of nasopharyngeal carcinoma (NPC).

Animal and human studies support the potential that formaldehyde’s effects at the portal-of-entry (POE) are general and not specific to a certain cell type or tumor development. This is consistent with the reactive nature of formaldehyde.

The majority of respiratory tract tumors reported in animal inhalation toxicity studies are squamous cell carcinomas derived from ciliated epithelial cells.(2-6) Polyploid adenomas have also been regularly observed, especially in the medial maxilloturbinates.(5, 7)

## Estimated regional absorption of inhaled formaldehyde in the nasal cavity based on computational fluid dynamic modeling (8)



## Genotoxic Action of Formaldehyde

### DNA Reactivity

- Formaldehyde interacts with DNA to form DNA protein crosslinks (DPX),
- FA-DNA adducts have been reported in several test systems
- In animal studies, DPX are formed in the nasal mucosa in a dose dependent fashion.(9-11)

### Formation of DPX is an indication of mutagenic action

- The direct formation of DPX in vitro has been demonstrated under conditions where mutations are observed, and below cytotoxic levels.(12)
- DPX is formed in vitro under conditions shown to result in mutagenesis and clastogenic effects.(13, 14)
- Even after DPX repair, there is evidence that DNA lesions remain which may result in DNA strand breaks or point mutations during mitogenesis.

### Formaldehyde induces clastogenic damage

- Formaldehyde exposure has been correlated to increased micronuclei and chromosomal aberrations in human buccal and oral cells that correspond to formaldehyde induced tumor sites.(15-19)

## Risk Assessment Implications

- Measurement of cell proliferation, DNA protein crosslinks, or genotoxicity may require examining a population of cells which have been subject to different degrees of formaldehyde absorption.
- When evaluating the tumor dose response, cells within the target tissue will represent a range of formaldehyde concentrations.
- The proposed integrated dose response curve will allow examination of different dose response relationships on which to base quantitative risk assessment.

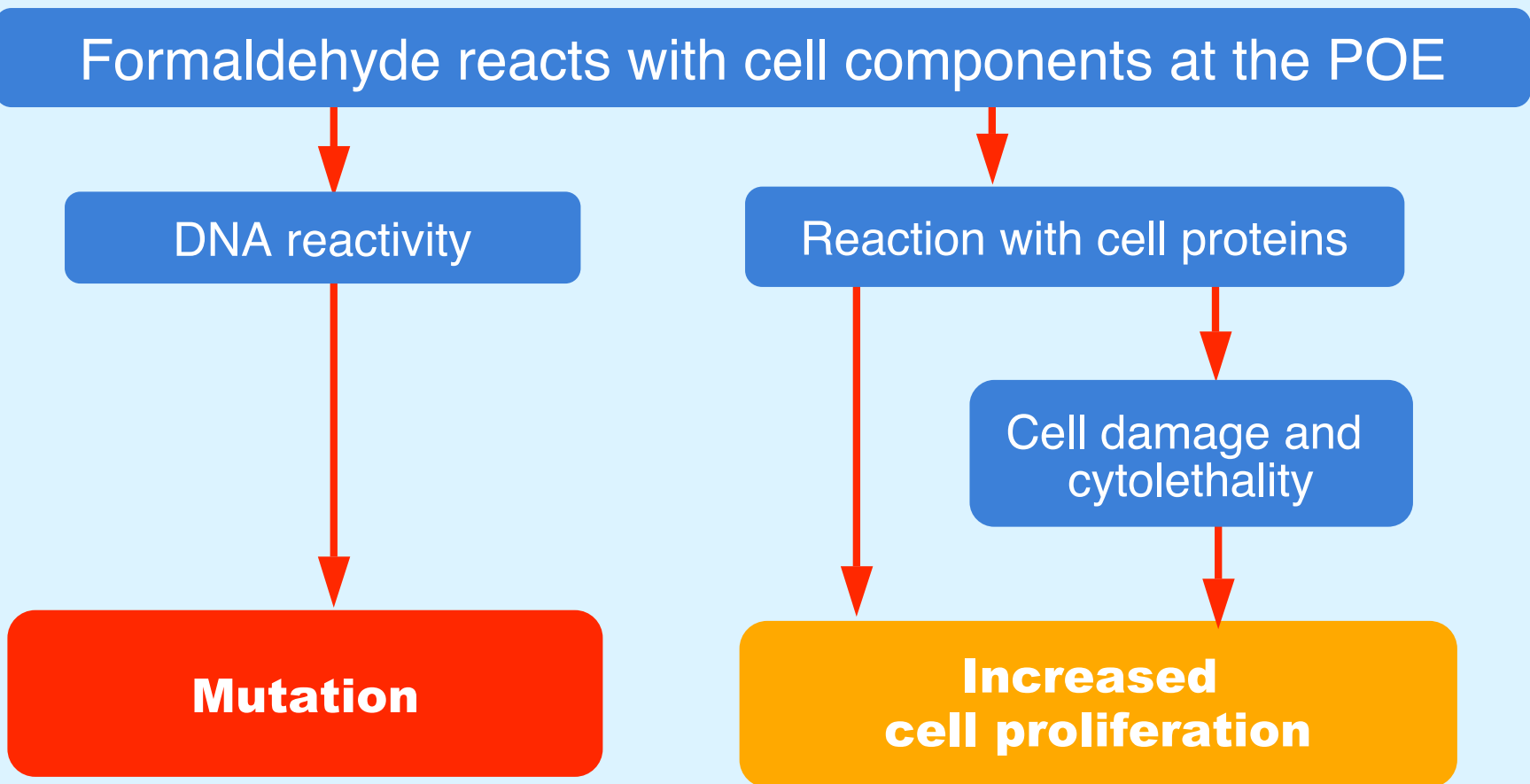
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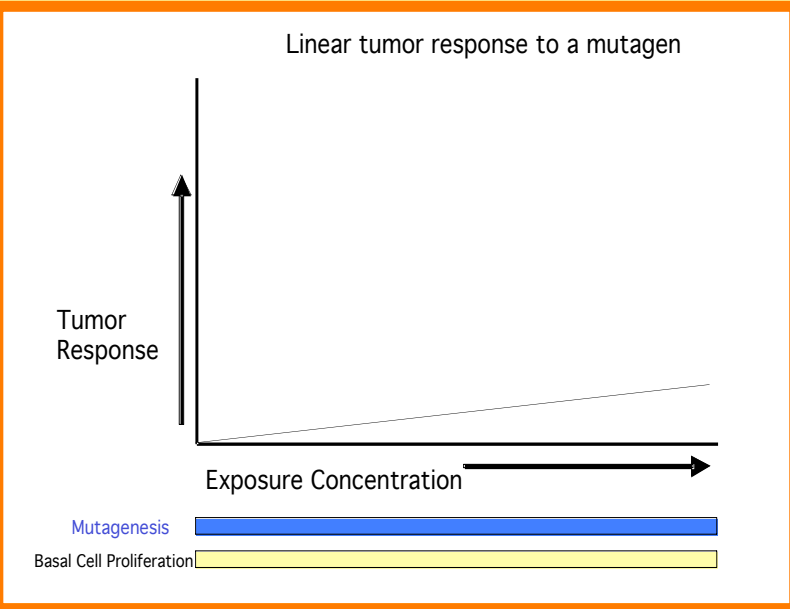
## Mode of Action Evaluation

The hypothesized carcinogenic mode of action for formaldehyde includes both genotoxic action and induction of cell proliferation as key events. The induction of cell proliferation allows an increased opportunity for mutations and reduced DNA repair as the time between cell cycles is reduced. At cytotoxic levels of exposure, cell death at the portal-of-entry (POE) leads to regenerative hyperplasia in the affected tissue.

### Key Events

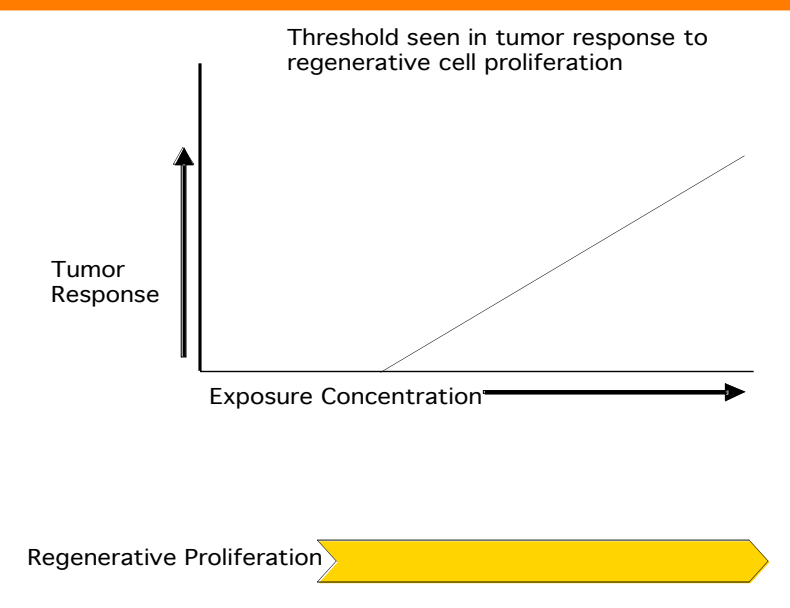


## Cell Proliferation as a Driver of Transformation



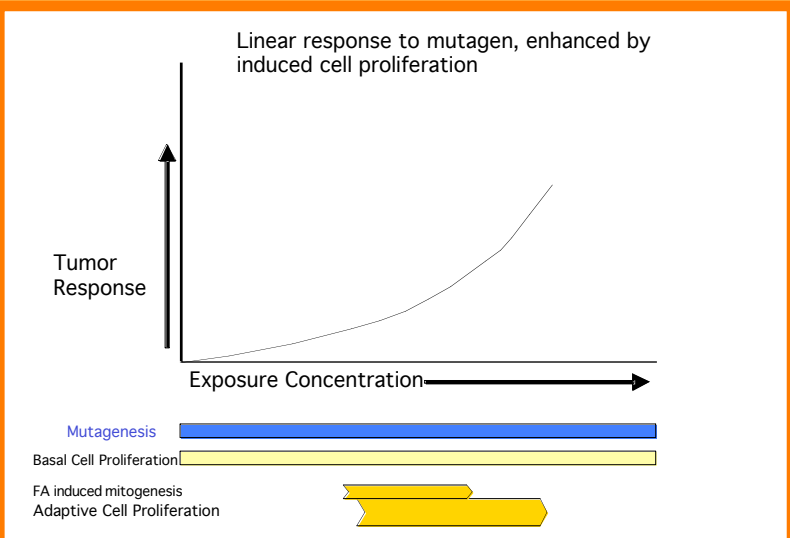
### Basal Cell Proliferation and FA-induced mutation

Figure 1: The dose response curve may be generalized as a linear curve with proportional response at each exposure level. The exact shape of the dose response curve is impacted by the induction of DNA repair mechanisms and the effectiveness of DNA protein crosslinks (DPX) to result in effective mutation.



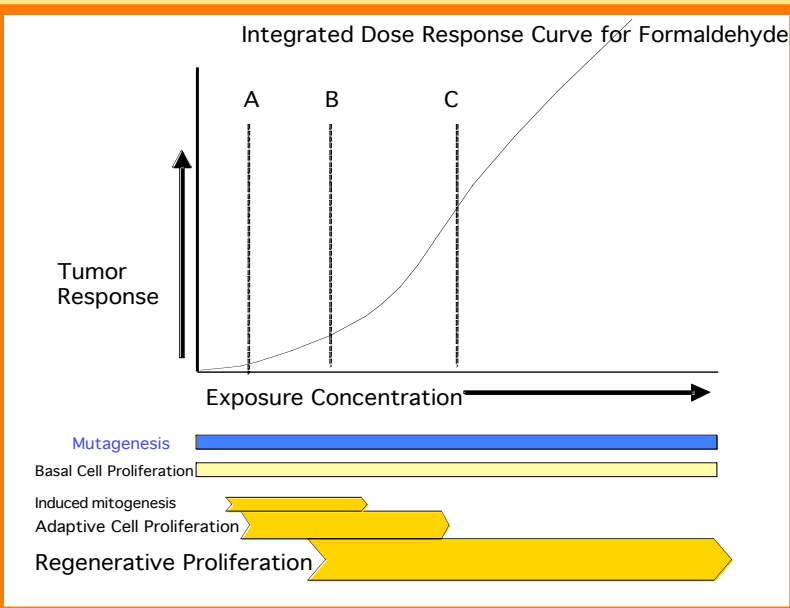
### Regenerative cell proliferation

Figure 2: In contrast, regenerative cell proliferation is generally considered a key event which would result in a threshold on tumor response with cytotoxicity.



### Formaldehyde induced proliferation

Figure 3: Other causes of mitogenesis, below where cytotoxicity is observed, would in theory increase tumor response in conjunction with formaldehyde induced mutation.



### Integrated dose response curve

Figure 4: When evaluating the tumor dose response, cells within the target tissue will represent a range of target tissue formaldehyde concentrations. Therefore, an integrated mode of action (MOA) scheme is hypothesized where key events may influence the observed tumor response differentially across the dose response range.